International Journal of Cardiology 276 (2019) 38–39

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Antithrombotic therapy after acute coronary syndromes in patients with atrial fibrillation: Shouldn't we pay more attention to the risk of ischemic and thromboembolic events?

José Luis Ferreiro *, Joan Antoni Gómez-Hospital

Heart Diseases Institute, Bellvitge University Hospital — IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

ARTICLE INFO

Article history:
Received 23 November 2018
Accepted 27 November 2018
Available online 29 November 2018

The management of antithrombotic therapy in patients with atrial fibrillation (AF) presenting an acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) is particularly complex. Oral anticoagulation (OAC) is superior to single or dual antiplatelet therapy (DAPT) for the prevention of thromboembolic complications (stroke and systemic embolism) due to AF, whereas DAPT with low-dose aspirin and a $P2Y_{12}$ inhibitor is the recommended antithrombotic treatment to prevent ischemic events (myocardial infarction and stent thrombosis) in patients with ACS or undergoing PCI. However, the choice of the antithrombotic regimen becomes a clinical problem when both situations coexist, because the so-called triple therapy (combination of OAC plus DAPT) is known to increase the risk of major bleeding by at least two to three times compared to DAPT [1]. Indeed, the optimal antithrombotic strategy in this scenario (ACS or PCI in patients needing OAC due to AF) is nowadays a matter of debate and controversy.

Current European and American guidelines recommend triple therapy (OAC plus DAPT with aspirin and clopidogrel) initially after PCI, with or without ACS, in AF patients requiring OAC after careful evaluation of ischemic and bleeding risks [2,3]. It is also recommended to keep triple therapy duration as short as possible and to consider dual antithrombotic therapy (OAC plus a single antiplatelet agent) after PCI instead of triple therapy only in patients in whom the bleeding risk prevail over the ischemic risk [2,3]. Conversely, a recent North American expert consensus document suggests dual therapy as the default strategy for most patients in this setting, while triple therapy is only considered up to 1 month in selected patients at high ischemic risk and low bleeding risk [4]. However, both strategies coincide with the need of OAC in this scenario since its net clinical benefit is undisputed in the majority of AF patients [5]. Despite guidelines recommendations, underuse of OAC therapy in patients with AF is not uncommon in real-world practice and even frequent in AF subjects presenting with ACS or undergoing PCI [6].

In this issue of the Journal, Cordero and colleagues investigated the long-term incidence of stroke in a two-center retrospective study of 8771 patients admitted with the diagnosis of ACS [7]. The prevalence of AF was 12.4% and the rates of stroke (92% were ischemic strokes) and mortality were more than two-fold higher in the group of patients with AF than in those without (7.8% vs. 3.3% and 10.2% vs. 4.4%, respectively), during a median follow-up of 58.7 months. The long follow-up of the study is indeed meritorious and allowed assessing that the median time to suffering the first stroke was 27 months in the overall population (5 months earlier in the AF group). Despite a worse prognosis in AF patients is expected, it is remarkable that OAC was prescribed at discharge in less than 50% of them, which is against guidelines recommendations. Nevertheless, this finding is in line with results from other "real-life" observational studies on patients with indication for OAC undergoing PCI or suffering an ACS, which have quite consistently shown that a strikingly low percentage of patients (often less than 50%) are actually prescribed OAC at discharge [6].

In recent landmark investigations conducted in patients with OAC indication undergoing PCI, namely the WOEST, the PIONEER AF-PCI or the RE-DUAL PCI trials, the focus has been put on finding antithrombotic regimens to reduce the risk of bleeding, which is indeed relevant [8–10]. However, these trials have somewhat tiptoed around the efficacy of these strategies to prevent ischemic and thromboembolic events. Actually, the three studies were clearly underpowered for any efficacy endpoint, including the risk of stroke. Of note, the prevention of ischemic stroke in AF is of outmost relevance because of its often severe and disabling consequences. OAC therapy is effective for prevention of thromboembolisms in AF patients and can even prolong life [5]. In fact, its benefit outweighs the increase in bleeding risk even in elderly and frail patients, with the exception of those with very low stroke risk.

Some reasons classically mentioned for not prescribing or stopping OAC are the occurrence of a bleeding event (although a minor or nuisance bleeding may not justify withholding therapy), a perceived high risk of bleeding (common when combining antiplatelet and anticoagulant agents), and a poor quality of anticoagulation with vitamin K antagonists

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.10.082.
* Corresponding author at: Heart Diseases Institute, Bellvitge University Hospital — IDIBELL, Feixa Llarga, 08907 L'Hospitalet de Llobregat, Barcelona, Spain.
E-mail address: jlferreiro@bellvitgehospital.cat (J.L. Ferreiro).

https://doi.org/10.1016/j.ijcard.2018.11.126

(VKAs), which clearly should not represent an issue in the era of direct oral anticoagulants (DOACs). DOACs are preferred by guidelines over VKAs in patients with non-valvular AF requiring OAC and undergoing PCI due to a more favorable bleeding risk [2]. An important remark when using DOACs in this clinical setting is that the lowest dose that has been tested and approved for stroke reduction should be used without unnecessary dose reductions. One of the reasons to explain why the reduced 15-mg dose of rivaroxaban of the PIONEER AF-PCI trial did not have a negative impact on the risk of stroke, in addition of being underpowered, could have been an insufficient 1-year length of follow-up (a longer median time to the first stroke was observed in the study by Cordero et al.). Unfortunately, information regarding quality of OAC (time in therapeutic range for subjects on VKAs), dosage of DOACs or changes in prescription of antithrombotic agents over time is not reported in the registry from Cordero et al., since it was not specifically designed to evaluate antithrombotic strategies in AF patients presenting with ACS.

Further investigation is warranted in order to help determining the optimal antithrombotic regimens in the complex scenario of AF patients requiring OAC and presenting with ACS and/or undergoing PCI. The ongoing AUGUSTUS (NCT02415400) and ENTRUST-AF PCI (NCT02866175) trials will provide interesting insights in the matter. Nevertheless, one may wonder whether the scientific community is nowadays just focusing in the decision of dropping or maintaining for a short time one antiplatelet agent to diminish the risk of bleeding, whereas not enough attention is being paid to ischemic events or to ensure appropriate long-term prevention of thromboembolic events in AF patients.

Conflict of interest

José Luis Ferreiro (corresponding author) reports a) honoraria for lectures from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, and Boehringer Ingelheim; b) consulting fees from AstraZeneca, Eli Lilly Co., and Ferrer; c) research grants from AstraZeneca.

Joan Antoni Gómez-Hospital reports a) honoraria for lectures from AstraZeneca, and Boehringer Ingelheim.

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